Chapter 4
Mechanisms of Acupuncture Analgesia

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Introduction

Acupuncture is an effective needling technique from traditional Chinese medicine dating back 3,000 years. Although historically it is been used to treat a variety of different health problems, including obesity, infertility, and colds, it is also commonly used to alleviate pain.

Acupuncture started gaining in popularity and acceptance in the late twentieth century as both a solo and an adjunct therapy for the treatment of pain. By the mid-1990s, support of both physicians and patients to integrate acupuncture into Western medical practice was growing [1]. In November 1997, on the basis of well-designed studies, the National Institute of Health (NIH) supported the use of acupuncture for pain, nausea, vomiting, and post-stroke dysfunction [2]. This increased awareness in the Western community has led to more evidence-based research to clarify the mechanism of acupuncture analgesia. Although there is no one clear pathway, this chapter will review recent literature and scientific theories.

Acupuncture and Traditional Chinese Medicine (TCM)

It is difficult to translate the mechanism of acupuncture analgesia in Western terms, because the philosophy of TCM is entirely different. In brief, TCM believes in the theory of holistic balance between the Yin and Yang and problems arise when there is an imbalance. Acupuncture is used to balance the Yin and Yang, which are

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manifested to regulate the Qi (energy)and blood. Qi travels through channels called meridians in the body. There are essentially 20 channels with access points, called acupuncture points, strategically aligned along the meridians, which can be manipulated through various techniques to achieve balance of the Qi. These techniques include acupuncture (percutaneous insertion of a fine needle), moxibustion (thermal therapy using the moxa roll herb), acupressure (deep pressure without dermatologic invasion), or electroacupuncture (EA) (electrical stimulation of needles at acupoints). Even with acupuncture alone there are specific techniques of twisting the needle side to side and up and down to capture the Qi. The practitioner often describes this capture, termed De Qi, as a sense of tightness around the needle as it enters deep tissues. In TCM, it is thought of as “the fish taking the bait” when the acupuncture point stimulates the imbalanced Qi. The sensation experienced by the patient is often soreness, numbness, heaviness, or even an electrical sensation. Acupuncture relieves pain and illness by unblocking stagnant Qi in the meridians, thereby restoring the balance between Yin and Yang.

Translating Acupuncture Analgesia in Terms of Western Medicine: Evidence-Based Research

Since the 1970s, there have been a growing number of evidence-based research studies employing a variety of different modalities, ranging from human and animal studies to those using technologically advanced imaging to investigate the mechanism of acupuncture analgesia. Arising theories from current literature describe a neural basis for its effect, involving the peripheral and central pain pathways.

Peripheral Mechanism

Sensory Fibers

One of the first human studies to scientifically investigate the effects of acupuncture was conducted in 1973, and tested the analgesic effects of acupuncture against morphine [3]. Two randomly divided groups of volunteers received either acupuncture at the acupoints for large intestine 4 (LI 4) and stomach 36 (ST 36) or morphine intramuscularly. Although both groups showed an increase of 80–90 % in their pain thresholds, researchers found that local anesthetic injection of 2 % procaine at LI 4 demolished any acupuncture effect or local sensation. Another study used direct stimulation of peripheral nerve sensory fibers and acupuncture needling. It showed that both raised the pain thresholds of the subjects in a similar manner [4]. This report not only supported the finding that acupuncture raises the pain threshold but also revealed evidence that acupoints may be related to peripheral nerve sensory fibers.

Deep Tissue Nerve Fibers

Clinical and observation studies of the similarities of acupuncture to the peripheral nervous system led to a topographic mapping of acupoints to their afferent nerve fibers. Zhou et al. [5] mapped 12 meridians, including Ren meridian, with its 324 acupoints, and saw that 323 had rich innervations. It was proposed that the effectiveness of acupuncture lies within deep tissue innervations and not superficial skin afferent fibers [6]. Volunteers in a study by Chiang et al. [7] experienced increased pain threshold with needling at acupoint LI 4. Procaine administered to the deep branches of the ulnar nerve and median nerve innervating LI 4 eliminated acupuncture-induced analgesia. However, procaine to the cutaneous branches of the radial nerve innervating LI 4 at the skin did not affect the analgesia. This study suggested that deep tissue innervation and not superficial afferents at the skin level are involved in acupuncture analgesia.

Muscle Tissue

Other studies revealing deep tissue mechanism s of acupuncture were derived from needling technique and achieving the De Qi sensation. Because of the twisting and pulling of the needle in the muscle, one proposed mechanism of acupuncture's analgesic effect focused on the afferent receptors in muscle and other deep tissues. This theory stemmed from small clinical and observational studies. Eleven patients had stimulation of ST 36 and subsequently experienced De Qi sensation and activity on electromyography [8]. However, both were abolished after lumbar epidural, leading researchers to conclude that acupoints had afferent muscle receptor innervation through spinal cord pathways.

Connective Tissue

Another theory to explain De Qi lies within the connective tissue itself. In acupuncture, the sensation of De Qi is described as a "fish taking the bait" and this may be a coupling action of the needle with connective tissues during the winding motion of insertion. Zhang et al. [9] found that stimulation of acupoint ST 36 generated analgesia and degranulation of mast cells. Pain relief was diminished with destruction of mast cells with disodium cromoglycate at the acupoint. Yu et al. [10] found similar results with destruction of the ST 36 collagen fibers with type I collagenase. These studies suggest that mast cells in connective tissues may play a role in acupuncture effectiveness.

Pain Fibers

A and C pain fibers relay sensory information from nociceptors and mechanoreceptors to the first order dorsal root ganglion, and subsequently synapse to second order neurons in the dorsal horn of the spinal cord. The sensory information is then transmitted through the anterolateral system, specifically the spinothalamic tract for pain and temperature, and the dorsal column–medial lemniscus system for mechanosensory input. Animal studies showed increased pain thresholds in both chronically dorsal chordotomized and control subjects, but unilateral ventral section of the spinal cord resulted in decreased effect in the contralateral side [11]. This suggested that the anterolateral system for pain and temperature sensation plays an important role in the acupuncture pathway.

Transmission of pain signals and acupuncture signals both require intact nociceptive afferent receptors. Pan et al. [12] showed that there was no response to pain in rats with receptor inhibition using capsaicin. A and C pain fibers have specifically been implicated as being related to acupoints. Li et al. [13] used Evans blue extravasation technique to map C fibers on rat hind limbs. The area of extravasation was in the distribution of acupoints and meridians. The authors concluded that acupoints were areas with high innervation, particularly with pain fibers.

The range of A-type afferents has been shown to illicit a lower nociceptive response in cat spinal dorsal horn neurons [14]. Specifically, EA can stimulate Aβ-type afferents alone to produce analgesia [15]. A recent study by Leung et al. [16] showed increased analgesia with activation of Aδ-type afferents by acupuncture.

C fibers also appear to play a role in acupuncture analgesia. Degeneration of unmyelinated C fibers using capsaicin showed decreased analgesia when acupuncture was introduced to rats [17]. In cat studies, C fiber activity persisted after termination of stimulation at ST 36 [18]. This may correspond to the clinical sensations of continued acupuncture effect for hours and days after treatment.

Acupuncture also uses the descending inhibitory pathway to enhance analgesia. Particularly, EA modulates the nucleus raphe magnus (NRM) of the descending inhibitory pathway to diminish the sensation of painful stimuli [19]. Liu and Wang found that lidocaine injection to the NRM stopped the antagonistic effect against analgesia produced by acupuncture [20]. This supported the notion that descending inhibitory pathways function to enhance acupuncture analgesia.

Central Mechanism: Molecules and Receptors

Opioids

Opioids, including β-endorphins, enkephalins, and dynorphins, are endogenous peptides that bind to μ-, δ-, and κ-receptors to create analgesia. Studies showed decreased acupuncture analgesia in rats that are opiate receptor deficient [21]. Specifically, Cheng and Pomeranz noted the possibility that different frequencies of EA elicited different mechanisms of analgesia [22]. With inhibition of opioid receptors, subsequent studies concluded that low frequency versus high frequency EA caused activation of different opioid receptors [23–26]. Low frequency (2–15 Hz) may release enkephalin, β-endorphin and endomorphins working on μ- and δ-opioid receptors. High frequency (100 Hz) caused release of dynorphin to κ-opioid receptors on the spinal cord.

However, hyperalgesic rats had analgesic effects through μ- and δ-opioid receptors at both low (10 Hz) and high (100 Hz) frequencies [27]. This is contrary to normal animal models that showed only μ- and δ-opioid receptors effect at low frequency and κ-opioid receptor at high frequency. Overall, acupuncture potentiates opioid release in its analgesic pathway, especially with different EA frequencies.

Cholecystokinin (CCK) Octapeptide

CCK-8 also has a significant role in acupuncture analgesia. Increase in CCK-8 via intrathecal injection in mice yielded less pain control under acupuncture, whereas CCK-8 receptor antagonism showed greater analgesia [28]. CCK-8 production is increased in subjects that do not show antinociceptive effects of acupuncture and decreased in those responding to acupuncture analgesia [29]. This suggested that CCK-8 and its receptor have a role in reducing the effects of acupuncture.

5-Hydroxytryptamine (5-HT)

5-HT, aka serotonin, is a neurotransmitter found in the gastrointestinal tract, platelets, and central nervous system. It helps modulate the sense of emotional well-being and decreases nociceptive pain primarily at the NRM in the brainstem. Dong and Jiang [30] showed increase in 5-HT at the NRM in rats with acupuncture analgesia. Further studies by Chang et al. [31] showed a significant decrease in acupuncture analgesia when 5-HT receptors were blocked. Both 5-HT1a and 5-HT3 antagonists blocked EA analgesia at low and high frequencies but 5-HT2 antagonists enhanced analgesia at high frequency (100 Hz). These studies indicated that acupuncture modulates 5-HT release for antinociceptive effects.

N-methyl-D-aspartic Acid (NMDA) Receptor

Glutamate and its receptors, such as the NMDA receptor, are part of the mechanism in the transmission of painful stimuli. Antagonism of NMDA receptors with agents such as ketamine and nitrous oxide, are known to reduce subjective pain and are common agents used in anesthesia and analgesia. EA reduced the expression of NMDA receptors in rats [32], and NMDA receptor inhibition enhanced the effects of acupuncture analgesia [33]. Research suggests that acupuncture may block NMDA receptor and decrease nociception.

Other Neurotransmitters

There are still various neurotransmitters under investigation. Many, including noradrenalin, γ-amino-butyric acid (GABA), and substance P have been implicated in the mechanism of acupuncture analgesia, but substantial data is lacking and sometimes contradictory. Few studies suggested that angiotensin, somatostatin, arginine vasopressin, and neurotensin may indirectly affect antinociceptive effects of acupuncture. Further studies will be needed to clarify their roles in acupuncture.

Cyclooxygenase-2 (COX-2) in Animal Models of Neuropathy and Inflammation

Recent studies suggested that acupuncture decreased the inflammatory process, thereby reducing pain. Using spinal cord glia, which plays a part in inflammation and neuropathic pain, Sun et al. [34] showed increased acupuncture analgesia when glia metabolism was inhibited. Mice induced with Parkinson's disease had decreased microglial and COX-2 activity with acupuncture [35]. The mechanism of acupuncture analgesia may include reducing inflammation via inhibition of glia cells and COX-2 enzymes.

Lau et al. [36] has shown that acupuncture may inhibit COX-2 in the spinal dorsal horn where COX-2 is upregulated after the development of neuropathic pain following spinal nerve ligation (SNL). After L 5 SNL, the rats were treated either with acupuncture applied to Zusanli (ST 36) and Sanyinjiao (SP 6) bilaterally with or without electrical stimulation (2 Hz, 0.5–1.2 mA) four times over 22 days, and/or celecoxib fed daily. EA had a long-lasting and better analgesic effect than celecoxib in reducing neuropathic hypersensitivity. Though COX-2 expression in the spinal dorsal horn by immunostaining was significantly reduced by acupuncture and celecoxib, the superior analgesic mechanism of acupuncture appears well beyond COX-2 inhibition alone.

Central Mechanism: Neurophysiology and Imaging Study

Research has implicated various areas of the brain activated by acupuncture to produce analgesia. Previous studies used blockage of neurotransmission or implementing lesions to determine areas affected in acupuncture analgesia. Newer imaging studies have further suggested that acupuncture and pain have common central pathways. However, these interactions are complex and are yet to be fully understood.

Older Studies

Different frequencies of EA activate different patterns of central nervous system (CNS) involvement. Lower frequency EA elicit a pathway following the arcuate nucleus, periaqueductal gray (PAG), NRM, and spinal cord [37]. At 100 Hz frequency, the PAG is also involved, but through activation of the parabrachial nucleus [37, 38]. Hence, low and high frequency EA both activate the serotonergic system, but through different mechanisms.

Acupuncture may activate the stress response through the hypothalamic–pituitary–adrenocortical axis, but through a different pathway. Pituitary research has shown that anterior pituitary cells are both activated by noxious stimuli and by EA, but that separate hypothalamic nuclei are involved, particularly the arcuate nucleus and adjacent nuclei in the mediobasal hypothalamus in EA [39]. The same researchers also found increases in adrenocorticotropic hormone (ACTH) and β-endorphin with both stimuli [40]. They concluded that EA activated a stress response via the hypothalamic–pituitary–adrenocortical axis, but with a different mechanism of action at the level of the hypothalamus. Lao et al. [41] saw increased glucocorticoid levels and longer analgesic effects at EA of 10 Hz versus 100 Hz, suggesting stronger and longer-lasting analgesia with low frequency EA.

Functional Resonance Magnetic Imaging (fMRI) Studies

The PAG plays a key role in the gate control theory of pain [42]. It serves to inhibit certain transmissions of nociceptive stimuli before reaching the cognitive areas that process pain. fMRI studies showed activation of the PAG during LI 4 acupuncture [43]. Sham acupuncture resulted in a decrease in PAG activity. Liu et al. concluded that acupuncture increased the inhibitory transmission of painful stimuli at the PAG area leading to decreased awareness of pain.

Acupuncture has been correlated to activity in the hypothalamus, specifically the arcuate nucleus and preoptic area. This includes fMRI studies of manual acupuncture stimulation [44], which also deactivates other areas of the limbic system known to process pain sensation. EA was also seen in fMRI studies to activate areas of the hypothalamus [45]. A follow-up study by Hui et al. [46] more specifically assessed the areas of brain involvement in subjects experiencing De Qi sensation, with and without sharp pain. Again, the hypothalamus, along with other areas of the limbic system, had decreased activity on fMRI. Besides the limbic system, which contributes to processing pain emotion, imaging studies have shown acupuncture-induced changes in other areas during analgesia as well. In a volunteer study, healthy subjects were exposed to cold pain and received either electrical or sham acupuncture [47]. Subjects in the electrical acupuncture group reported less pain and had fMRI imaging showing activity in the somatosensory areas, medial prefrontal and dorsal anterior cingulated cortices. This suggests that acupuncture analgesia may have a role in modulating the emotional and sensory areas that help process pain sensations.

More recent fMRI data showed cortical and subcortical activity with manipulation of acupuncture points compared with sham points. Eighteen healthy subjects without known neurological or psychiatric histories participated in both sham acupuncture and true acupuncture at ST 36 two days later [48]. Sensations related to the De Qi effect were correlated with imaging. A combination of conventional general linear model (GLM) and independent component analysis (ICA) was used to analyze the fMRI images. The De Qi sensation and prolonged acupuncture benefits had statistically significant effects on the anterior cingulated cortex, ventrolateral prefrontal cortex, supplementary motor area, primary and secondary somatosensory cortices, occipital cortices, and the midbrain.

Interestingly, propofol-based anesthesia reduced the cerebral response caused by acupuncture stimulation. fMRI studies of volunteers receiving acupuncture at ST 36, both awake and under anesthesia, in a pair *t*-test crossover study showed decreased cerebral involvement [49]. There were less blood oxygenation level-dependent signals induced by acupuncture under propofol anesthesia in the thalamus, red nucleus, insula, periductal gray, and auditory areas of the brain. Cerebral depression with propofol interferes with acupuncture's effects on the brain.

More recent research has also suggested a top–down mechanism of acupuncture analgesia. Areas of cognitive processing and emotional evaluation, including the second somatosensory area (SII), insula, dorsomedial prefrontal cortex, posterior cingulate, and precuneus, have been implicated using fMRI [50]. Subjects stimulated at PC 6 acupoint were asked to rate their sensations for real versus sham acupuncture. Imaging studies were correlated with the degree of subjective stimulation. The authors concluded that acupuncture may have a mind–body component directed by somatosensory stimulation.

Positron Emission Tomography (PET) Studies

Current sophisticated technology has allowed further insight into areas of cerebral involvement. Harris et al. [51] used PET imaging to compare traditional acupuncture and sham acupuncture. Patients with fibromyalgia were given either traditional acupuncture or sham acupuncture for eight weeks. PET imaging was done at baseline and on week 4 after eight treatments. The results showed μ-opioid receptor binding in the cingulate, insula, caudate, thalamus, and amygdale in both the short and long terms. These effects were not seen in the sham treatment group. The traditional acupuncture group also experienced less pain associated with the increased long-term μ-opioid receptor binding potential.

Single-photon emission computed tomography (SPECT) and PET showed differences in brain perfusion and glucose metabolism after EA at LI 4 and large intestine 11 (LI 11) compared with baseline [52]. Areas involved include the left middle frontal gyrus, the superior parietal gyrus, the right superior frontal gyrus, and the middle parietal gyrus in the SPECT imaging and left superior medial frontal gyrus, the middle frontal gyrus, and the right superior medial frontal gyrus in PET imaging.

Park et al. [53] used fluorodeoxyglucose positron emission tomography combined computed tomography (FDG PET/CT) to analyze specific areas of brain involvement during acupuncture stimulation of LR 3 and ST 44 as compared with baseline. They found increased glucose metabolism in the left insula, bilateral thalami, superior frontal region of the right frontal lobe, and the inferior frontal region of left frontal lobe. However, the left cingulate and parahippocampal areas had decreased metabolism. They concluded that different areas of the brain during acupuncture are identified using FDG PET/CT imaging.

Clinical Implications

The numerous clinical applications of acupuncture and the selection of acupoints and techniques are beyond the scope of this chapter. However, the mechanism of acupuncture stimulation may have an impact on its effectiveness. Lang et al. [54] evaluated the immediate effects of different forms of acupuncture on thermal, mechanical, and vibratory sensory thresholds by quantitative sensory testing (QST) in 24 healthy volunteers. The heat pain threshold was increased after manual acupuncture on the treated and untreated side was compared with baseline. Low- and high-frequency electrostimulation led to a higher mechanical pain threshold on the treated side compared with baseline and manual acupuncture. The pressure pain threshold was also increased by all forms of acupuncture on both sides, with individual changes from baseline ranging from 25 to 52 %.

Schliessbach et al. [55] conducted a blinded, placebo-controlled, crossover study to investigate effects of brief manual and electrical stimulation of acupuncture points LI 4 and LI 11 on pressure pain detection thresholds (PPDT), compared with nonpenetrating sham acupuncture (NPSA). EA produced higher PPDT elevation than manual acupuncture and acupuncture in general showed significantly better analgesic effect than NPSA. These effects seemed to be short lasting (5 min) in the context of only brief acupuncture. The advantage of acupuncture to NPSA provided further evidence for acupuncture-specific analgesic effects. EA induced a significantly greater analgesia and less intense pain during stimulation during a brief needle application, compared with manual acupuncture. With the decrease in pain during the procedure and more effective analgesia, this study showed EA to be preferable to manual stimulation in providing acupuncture analgesia.

EA has more recently been shown to have differing effects when employing low versus high frequency stimulation. Zhou et al. [56] studied the effects of acupuncture on the sympathoexcitatory response in rats. They compared manual acupuncture at 2 Hz with low (0.3–0.5 mA at 2 Hz), medium (0.3–0.5 mA at 40 Hz), and high (0.3–0.5 mA at 100 Hz) frequency EA at pericardium 5–6 (P 5–6), Spleen 36–37 (S 36–37), and heart 6–7 (H 6–7) testing cardiovascular reflexes. The cardiovascular pressor reflex response was inhibited with manual acupuncture and low frequency EA, and no difference was seen with medium or high frequency stimulation. Also, stimulating two acupoints that independently decreased reflex response did not produce an additive effect. This suggests that low frequency acupuncture via manual or electrical stimulation may be adequate for effective acupuncture treatment and that multiple acupoints to obtain the same treatment may not be necessary.

Duration of EA also plays a role in effective acupuncture analgesia. Cold thermal pain thresholds were tested in healthy volunteers by alternating between 2 and 100 Hz at 5 mA for durations of 0, 20, 30, and 40 min. Thirty minutes of EA stimulation resulted in the highest threshold, lasting for at least 60 min. Wang et al. [57] suggested that a 30 min duration was the most effective amount of time for producing acupuncture analgesia.

Summary

Acupuncture is a long-practiced mode of treating pain, based on the traditional Chinese medicine theory of the balance of Yin and Yang. While difficult to translate and poorly understood in Western scientific terms, research over the past few decades has shown correlations between acupuncture and neural pathways, including afferent peripheral nerve transduction and transmission, ascending and descending nerve routes, and central processing in the brain. Animal studies and new imaging techniques have yielded insight into acupuncture analgesia even at the molecular level and shown varying areas of modulation in central nervous system. Despite the lack of a clear consensus about the mechanism of its effect on analgesia, acupuncture has been shown to be beneficial in pain management. Clinical research may guide frequency and duration of EA for more effective and systematic treatment. Further research still needs to be conducted to better elucidate the mechanism of acupuncture analgesia.

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